

UNITED STATES PATENT APPLICATION

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Itraconazole Immediate Release Formulation

FIELD OF THE INVENTION

The present invention relates to the field of oral dosage forms. More particularly, it relates to an immediate release
5 oral dosage form of an antifungal for the treatment in mammals of fungi and related ailments.

BACKGROUND OF THE INVENTION

There exists a need for an orally administrable
10 antifungal medication with a high concentration of active ingredient that can be manufactured in an economically feasible manner. U.S. Pat. No. 5,633,015 (incorporated herein by reference) describes oral pharmaceutical formulations containing itraconazole beads that are seal coated.
15 Furthermore, a specific core size must be used to make the beads. A seal coat is generally employed for protection of the active ingredient or drug during processing and to reduce unwanted reactions. However, a seal coat also increases manufacturing time and costs.

20 Antifungal agents have been shown to be advantageous in the treatment of nail and skin fungus infections. Antifungal compositions are well known in the art. Specifically, U.S. Pat. No. 4,267,179, which describes the synthetic triazole antifungal compound itraconazole, 4-[4-[4-[4-[[2-(2,4-
25 dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3H-1,2,4-triazol-3-one, molecular formula $C_{35}H_{38}Cl_2N_8O_4$; and U.S. Pat. No. 4,916,134, which describes itraconazole's difluoro analog, saperconazole, 4-[4-[4-[4-[[2-
30 (2,4-difluorophenyl)-2-(1H-1,2,4-triazol-1-ylmeth yl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]-phenyl]-2,4-dihydro-2-(1-methoxypropyl)-3H-1,2,4-triazol-3-one, molecular

formula $C_{35}H_{38}F_2N_8O_4$ (see *The Merck Index* p.5263 and 8435, 13th Ed. (2001) and *Physicians' Desk Reference* 1313-1315, 38th Ed. (1998)). Both patents are incorporated herein by reference.

5 Itraconazole has a molecular formula of $C_{35}H_{38}Cl_2N_8O_4$ and a molecular weight of 705.64. It is insoluble in water, very slightly soluble in alcohols and freely soluble in dichloromethane. Additionally, it has a pKa of 3.70 (based on extrapolation of values obtained from methanolic solutions).

10 The drug itraconazole is commercially available in capsules, injections, and oral solutions (SPORANOX[®]). See Physician Desk Reference 55th Ed., pp. 1584-94 (which is incorporated herein by reference).

SUMMARY OF THE INVENTION

15 The present invention overcomes the drawbacks of the prior art through the novel development of an oral antifungal dosage form without the need of a seal coat, and without the limitation of a specific starting seed size. The lack of a seal coat substantially reduces manufacturing time and costs.

20 The foregoing advantages are obtained by a preparing an active pellet comprising:

- a) an inert starting seed;
- b) an anti-fungal agent;
- c) a binder; and optionally
- 25 d) an alkaline agent.

The active pellets without a seal coat can be mixed with conventional tableting excipients and compressed into a tablet or loaded into a capsule for oral administration.

30 The present invention also relates to a method of producing the pellets or beads.

In a preferred embodiment of the present invention an organic solvent system is used to apply the drug layer to the inert starting seed.

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DETAILED DESCRIPTION OF THE INVENTION

In the present invention, the inert starting seed is a sugar seed with a mesh size of 15-40, preferably 18-20. The
10 inert starting seed must be of sufficient density and strength to enable it to undergo coating in a fluidized bed process. Suitable starting seeds are sugar seeds or non-pariels that are well known in the art. Additional suitable starting seeds may be chosen from plastic resins, silica, glass,
15 microcrystalline cellulose, hydroxyapatite, sodium chloride, potassium chloride, calcium carbonate, magnesium carbonate, activated carbon, citric acid, fumaric acid, tartaric acid, ascorbic acid, oligosaccharides, glucose, rhamnose, galactose, lactose, sucrose, mannitol, sorbitol, dextrin, maltodextrin,
20 cellulose, sodium carboxymethyl cellulose and starch. The preferred starting seed is a sugar sphere with a mesh size of 18-20.

The pharmaceutically active ingredient or drug that is applied to the inert starting seed is itraconazole or its
25 difluoro analog, saperconazole.

In order for the drug to be applied to the inert starting seed, a binding agent may be necessary. The binding agent employed in preparation of the active pellet in accordance with the present invention can be any type of binding agent
30 commonly known in the art. Examples of some of the preferred binding agents are polyvinyl pyrrolidone, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyacrylate, ethylcellulose, or mixtures of

the foregoing. In the preferred embodiment of the present invention, the binding agent is hydroxypropyl methylcellulose (available as METHOCEL® E5).

The drug is applied to the inert starting seed by any conventional techniques known in the industry, such as, pan coating, roto-granulation or fluidized bed coating. During such coating operations the drug is dispersed or dissolved in an organic solvent, which may also contain other conventional excipients, such as the above mentioned binding agent.

Representative examples of the alkaline agent that may be used in preparation of the present invention are amino acids, such as lysine, arginine, ornitine, histidine, organic buffering compounds such as trometamine (i.e. Tris-buffer), N-amino sugars such as N-methyl-D-glucamine (i.e. Meglumine), N-ethyl-D-glucamine (i.e. Eglumine), glucosamine, disodium-N-stéaroyl-glutamate, heterocyclic amine derivatives such as piperazine or its hexahydrate, N-methylpiperazine, morpholine, 1-(2-hydroxyethyl)pyrrolidine, alkali salts of citric acid, tartaric acid, caproic acid or fatty acids, alkali metal phosphates, silicates or carbonates, sodium, potassium, magnesium, calcium or aluminium hydroxides and organic amines such as ethylamine, dicyclohexylamine or triethanolamine, or alkaline ammonium salts.

The weight percentages of ingredients in the present invention based on the final pellet composition can be seen in the following table.

Table I

Ingredients	Preferred	Most preferred
Inert seed	At least 35%	35-55%
drug	10-50%	15-40%
binder	10-50%	25-40%
alkaline agent	0-5%	0-3%

The tablet or capsule containing the active pellets prepared in accordance with the present invention should obtain its peak plasma level within about 3 to 9 hours, preferably about 3.5 hours to about 6.5 hours and have a C_{max} of less than 100 ng/ml, preferably less than 90 ng/ml, and most preferably between 40 ng/ml and 80 ng/ml.

DESCRIPTION OF THE PREFERRED EMBODIMENT

The present invention will be further illustrated by the following examples.

EXAMPLE I

An immediate release itraconazole capsule in accordance with the present invention is prepared as follows.

Stage I Drug Solution

70.25 kg of methylene chloride is placed in a 30-gallon stainless-steel tank with 46.83 kg of Ethanol SDA 3A 190 Proof. Next, 6.109 kg of hydroxypropyl methylcellulose (Methocel® E5) is added into the previously formed organic solvent and mixed for at least 30 minutes. Subsequently, 4.072 kg of itraconazole is added to the above mixture and mixed for at least 20 minutes.

Stage II Spray Coating

7.819 kg of sugar spheres NF 18/20 are placed into a fluidized bed coater. The sugar spheres should be preheated for 3 minutes at an inlet air temperature of $55^{\circ}\text{C} \pm 5^{\circ}\text{C}$. The drug suspension prepared above is sprayed onto the sugar seeds under the following conditions:

Table II

Fluidized Bed Coater	Bottom Spray with Wurster insert
Nozzle tip diameter	1.8 mm
Shaking interval	1 min
Shaking Duration	3 sec
Atomization Pressure	2-3 bar
Inlet Air Temperature	$55-60^{\circ}\text{C}$
Pump Rate	15-150 mL/min
Tubing Size	24 mm

The drug solution should be sprayed slowly at the beginning to avoid agglomeration of the sugar spheres. As the spraying continues the rate of drug application can be increased.

Once the drug suspension has been consumed the pellets are dried for 20 minutes or until the loss on drying (LOD) is less than 1%. The pellets are then placed on trays in one-half inch layers and dried in an oven at 75°C for at least 40 hours.

Stage III Encapsulation

The itraconazole pellets are dusted with 0.360 kg of talc and encapsulated utilizing equipment and guidelines commonly known in the art. Natural/Aqua blue opaque size "0" capsules

are filled with itraconazole pellets, which contain 100 mg of itraconazole.

EXAMPLE II

- 5 An immediate release itraconazole capsule in accordance with the present invention is prepared as follows.

Stage I Drug Solution

- 70.25 kg of methylene chloride is placed in a steel 30-
10 gallon drum with 46.83 kg of Ethanol SDA 3A 190 Proof. Next, 6.109 kg of hydroxypropyl methylcellulose (Methocel[®] E5) is added into the previously formed organic solvent and mixed for at least 30 minutes. Subsequently, 4.072 kg of itraconazole is added to the above mixture and mixed for at least 20
15 minutes. 0.081 kg of L-arginine base is added into 0.459 kg of purified water and mixed for 20 minutes and then added to the above mixture.

Stage II Spray Coating

- 20 7.738 kg of sugar spheres NF 18/20 are placed into a fluidized bed coater. The sugar spheres should be preheated for 3 minutes at an inlet air temperature of 55°C ± 5°C. The drug suspension prepared above is sprayed onto the sugar seeds using the conditions and parameters described in Example I.
25 Once the drug suspension has been consumed the pellets are dried for 20 minutes or until the loss on drying (LOD) is less than 1%. The pellets are then placed on trays in one-half inch layers and dried in an oven at 75°C for at least 40 hours.

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Stage III Encapsulation

The itraconazole pellets are dusted with 0.360 kg of talc and encapsulated utilizing the equipment and guidelines commonly known in the art. Natural/Aqua blue opaque size "0" capsules are filled with itraconazole pellets, which contain 100 mg of itraconazole.

EXAMPLE III

An immediate release itraconazole capsule in accordance with the present invention is prepared as follows.

Stage I Drug Solution

70.25 kg of methylene chloride is placed in a steel 30-gallon drum with 46.83 kg of Ethanol SDA 3A 190 Proof. Next, 6.109 kg of hydroxypropyl methylcellulose (Methocel[®] E5) is added into the previously formed organic solvent and mixed for at least 30 minutes. Subsequently, 4.072 kg of itraconazole is added to the above mixture and mixed for at least 20 minutes.

Stage II Spray Coating

7.819 kg of sugar spheres NF 25/30 are placed into a fluidized bed coater. The sugar spheres should be preheated for 3 minutes at an inlet air temperature of 55°C ± 5°C. The drug suspension prepared above is sprayed onto the sugar seeds using the conditions and parameters described in Example I.

Once the drug suspension has been consumed the pellets are dried for 20 minutes or until the loss on drying (LOD) is less than 1%. The pellets are then placed on trays in one-half inch layers and dried in an oven at 75°C for at least 40 hours.

Stage III Encapsulation

The itraconazole pellets are encapsulated utilizing the equipment and guidelines commonly known in the art.

- 5 Natural/Aqua blue opaque size "0" capsules are filled with itraconazole pellets, which contain 100 mg of itraconazole.

- 10 A biostudy between the above product and the SPORANOX[®] reference product using 29 individuals under fasting conditions produced the following results:

Table III

	Test Mean	%CV	Ref Mean	%CV	G-mean Ratio	90% C.I.	90% C.I.	Mid
Cmax	51.13	69.21	37.20	65.96	1.328	109.00%	162.27%	135.64%
AUC 0~t	586.86	70.90	433.70	66.69	1.319	110.73%	156.91%	133.82%
AUC 0~inf	644.09	71.93	477.48	65.58	1.313	110.99%	155.06%	133.02%
Tmax	3.86	26.55	3.72	25.77	1.034			

- 15 A biostudy using 19 individuals between the above product under fed and fasting conditions and the SPORANOX[®] reference product under fed conditions produced the following results:

Table IV

Test Fed/ Reference Fed	Test Mean	%CV	Ref Mean	%CV	G-mean Ratio	A-mean Ratio
Cmax	70.13	49.01	57.35	42.72	1.174	1.409
AUC 0~t	709.17	41.75	561.18	45.68	1.274	1.452
AUC 0~inf	745.97	41.36	594.83	45.91	1.265	1.436
Tmax	5.26	8.60	5.21	10.27	1.012	1.017

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While certain preferred and alternative embodiments of the invention have been set forth for purposes of disclosing the invention, modifications to the disclosed embodiments may occur to those who are skilled in the art. Accordingly, this specification is intended to cover all embodiments of the invention and modifications thereof which do not depart from the spirit and scope of the invention.